



DEPARTMENT OF HEALTH AND HUMAN SERVICES

TELECONFERENCE MEMORANDUM

Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Date\Time: March 13, 2007

CBER Representatives: Peter Bross, Boguang Zhen *Boguang Zhen*

Sponsor's Representative: Elizabeth Smith, Mark Frohlich, Lianng Yuh

STN : 125197/0

Subject: Clinical and Statistical Questions

Discussion:

The purpose of the call is to improve understanding of some of the analyses in the briefing documents and discuss some potential differences between FDA and Dendreon.

1. The date of unblinding the database for progression should be July 2002 not June 2002 (page 23 of clinical and pages 22 and 27 of statistical document).

This was due to the error in the sponsor's submission. In Appendix 16.1.9.10, the sponsor stated that data were unblinded in June 2002. The sponsor has informally submitted a corrected date via Email and will submit a formal amendment for the correction. FDA agreed to change the date.

2. Survival curves including 8 patients with deaths after 36 months in the clinical document (page 25)

Dendreon pointed out that they believed the survival curves presented in the clinical briefing document should be treated as supportive since no follow-up data were available for those who were alive after 36 months. The primary p-value for survival analysis should be presented as 0.010, not as 0.011 in the document. FDA agreed to present 36-month follow-up survival data as the main result and data including deaths after 36-month could be treated as supportive.

3. Use of Cox multiple regression model to adjust for baseline prognostic factors.
 - a. Covariate adjusted analyses – continuous vs categorical variables
 - b. Covariate adjusted analyses - choice of covariates

c. Impact of patients with missing covariates

The sponsor stated that, in general, continuous variable should be treated as continuous in the model and asked for justification of converting continuous into categorical variables in the Cox model in Table 9 of the statistical briefing document. FDA responded that these analyses are sensitivity analysis in order to see if the hazard ratio would change to either direction after adjusting for different imbalance between the two arms. It is not always the case that continuous variables should be treated as continuous in the model. There are pros and cons of doing that. In Cox model (I) of Table 9 (the sponsor's model), the sponsor also treated number of bone metastases as categorical variable instead of continuous. For Gleason score, cut-off point 8 is very important because the sponsor used it to modify an ongoing Phase III trial (D9902). The categorical variable for PSA was selected from the database the sponsor provided. It may reflect three levels of PSA (low, intermediate, high).

Regarding the choice of covariates, it is difficult to judge which set of covariates is optimal, but one can see that different set of covariates in the model could result in different p-values ranging from statistically significant to non-statistically significant.

The sponsor told FDA that while they agreed that the missing subjects in their model [Cox model (I)] could be biased in favor of the claim, missing subjects in Cox model (II)-(V) in Table 9 could be biased against the claim. Using continuous variables in these models decreased p-values and increased hazard ratios. FDA responded that these results were expected and this clearly indicates that one can easily select any results for her/his own favor from post-hoc analyses.

4. Correlation between CD54 upregulation and overall survival

- a. Study 1 vs Integrated Studies 1 & 2
- b. Continuous vs dichotomous analysis

Data showing relationship of Survival and CD54 were presented in the FDA and sponsor briefing document. The Sponsor expressed a preference for analysis by continuous variables, as this made the correlations appear more significant. FDA had no comments or preferences between these two types of analyses.

The sponsor also brought up the issues of whether survival analysis is pre-specified or not and cited several places in the protocols that they did mention survival analysis. FDA responded that it totally depends on the definition of pre-specification. If pre-specification requires 1) the endpoint for the analysis is well defined, 2) the primary statistical analysis is well specified, and 3) alpha level for hypothesis testing is well allocated, the survival analysis was not pre-specified in both Phase III studies. Based on this definition, for un-prespecified survival analysis in Study 9901, no one were sure if $p=0.01$ was statistically significant or not at the 0.05 level because we did not know how the alpha level was allocated for survival. From a hypothesis testing point of view, this was not statistically significant since 0.05 was allocated to the primary endpoint. Once failed to meet the primary endpoint, there was only zero alpha left and any p-value greater than zero would be considered non-statistically significant. However, if just mentioning survival analysis could be treated as pre-specification as the sponsor pointed out, the survival analysis may be considered as pre-specified in a very vague sense in both studies. But this type of pre-specification definition has nothing to do with evaluating the survival analysis results. Stating

this type of pre-specification would not be helpful for the difficulty of estimating Type I error rate for both trials.

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